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Review

Assessment of thermal dehydration using the human eye: What is the potential?

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ABSTRACT

Human hydration assessment is a key component for the prevention and proper treatment of heat-related fluid and electrolyte imbalances within military, sports and clinical medicine communities. Despite the availability of many different methods for assessing hydration status, the need for a valid method or technology that is simple, rapid, non-invasive, universal (detects both hypertonic and isotonic hypovolaemia) and is applicable for static (single point in time) and dynamic (change across time) hydration assessment is widely acknowledged. The eye is one candidate body region that might afford such a measure given the intricate balance between ocular dynamics (tear and aqueous humor formation) and blood (plasma osmolality and volume), which is considered the criterion measure for hydration assessment. The aim of this review is to introduce and discuss the potential for using ocular measurements for non-invasive hydration assessment, including tear fluid osmolarity (Tosm), non-invasive tear break-up time (NITBUT) and intraocular pressure (IOP). There is a relevant physiological basis for testing the merit of ocular measures for human hydration assessment and recent data indicate that Tosm and IOP may have utility. Further investigations are warranted to determine the degree to which ocular measures can act as accurate and reliable non-invasive hydration status markers.

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Contents

1. Introduction

Human hydration assessment is a key component for the prevention and proper treatment of fluid and electrolyte imbalances (Cheuvront and Sawka, 2005; Institute of Medicine, 2005; Mange et al., 1997; Sawka et al., 2007). The most common body water deficit (hypohydration) occurring in clinical, athletic and most military situations results from a net loss of hypotonic body fluids stemming from heat stress (sweating) and fluid restriction or fluid unavailability (Cheuvront et al., 2010; Institute of Medicine, 2005; Mange et al., 1997; Sawka et al., 2007). A rise in plasma osmolality is the hallmark of this hypertonic-hypovolaemia (Cheuvront et al., 2010; Feig and McCurdy, 1977), and the hypothalamus responds to these alterations by increasing arginine vasopressin hormone (AVP), which reduces urinary water loss and results in the production of more concentrated urine (Andreoli et al., 2000; Robertson et al., 1973). These physiological changes provide the framework for using blood and urine for

Abbreviations: Tosm, Tear fluid osmolarity; TBUT, Tear break-up time; NITBUT, Noninvasive tear break-up time; IOP, Intraocular pressure

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hydration assessment. However, when substantial solute is lost, such as during cold or high altitude exposure and in many medically relevant scenarios (e.g., gastroenteritis, hyperemesis), less 'free water' (i.e. water lacking solute) is cleared (Mudge and Weiner, 1970; Nose et al., 1988) and the resulting isotonic or hypotonic-hypovolaemia can go undetected using the same measures (Cheuvront and Sawka, 2005; Institute of Medicine, 2005; Mange et al., 1997; Sawka et al., 2007). Although no method can yet be universally applied to all types of hypohydration (hypertonic, isotonic and hypotonic hypovolaemia), many methods for assessing hydration state have been used. The optimal choice will depend on the nature of the fluid losses, measurement circumstances (field versus laboratory), the potential for confounding influences and the degree of acceptable invasiveness (risk/benefit) (See Cheuvront and Sawka, 2005 for a review of these methods).

Currently, the most accurate methods to assess hydration status in clinical, athletic, and military settings utilizes dynamic hydration assessment from blood, urine, or cardiovascular (orthostatic) markers (Cheuvront et al., 2010; Cheuvront et al., 2011; Cheuvront and Sawka, 2005, Duvekot et al., 1994; Knopp et al., 1980; Levitt et al., 1992; Mange et al., 1997; McGee et al., 1999). Although change can provide good diagnostic accuracy it requires a valid baseline, control over confounding variables, and often multiple invasive blood or urine measures (Carvajal, 1980; Cheuvront et al., 2010). Large population heterogeneity explains, in part, why few hydration status markers demonstrate nosological sensitivity from a more practical, static (single point in time) measure (Cheuvront et al., 2010; Levitt et al., 1992). There is currently no method or technology that is simple, rapid, non-invasive (Armstrong, 2005; Institute of Medicine, 2005), universal (detects both hypertonic and isotonic hypovolaemia), and is applicable for static and dynamic hydration status assessment (Cheuvront et al., 2010). For these reasons, the Institute of Medicine (2005) encourages more research to improve upon hydration assessment methods for the judicious diagnosis and treatment of hypohydration.

Measurements of the eye (e.g. tear quality, pressure) can be influenced by both volume and osmolality changes in blood (Ashkenazi et al., 1992; Gaasterland et al., 1979; Patel and Blades, 2003; Visscher and Carr, 1944), the latter of which is the current criterion measure for static hydration assessment of hypertonic-hypovolaemia (Cheuvront et al., 2010; Feig and McCurdy, 1977); as such, one or both hypovolaemia subtypes may be diagnosed with non-invasive human eye measures (Fortes et al., 2011; Kayikcioglu et al., 1998; Martin et al., 1999). A paucity of research exists that examines the potential for using ocular measures for hydration assessment (Fortes et al., 2011; Hunt et al., in press; Kayikcioglu et al., 1998) Therefore, the aim of this review is to discuss three ocular measurements that may have the potential for use as non-invasive hydration assessment markers, including tear fluid osmolarity (Tosm), non-invasive tear break-up time (NITBUT) and intraocular pressure (IOP).

2. Aspects of ocular anatomy and physiology applied to hydration status assessment

A simplified schematic of human eye anatomy is drawn in Fig. 1A. The tear film and aqueous humor are detailed hereafter for a better understanding of how their measurement may be used and interpreted for hydration assessment. The tear film is composed of mucous, aqueous and lipid layers that act to lubricate and protect the eyeball (Oyster, 1999). The lacrimal gland (Fig. 1C) secretes electrolytes, water, protein and mucin into the tear film under tight neural control (Dartt, 2009) (Fig. 2). This occurs in two stages, firstly in the acinar cells and secondly in the ductal cells. Acinar cells comprise about 80% of the lacrimal gland and secrete primary lacrimal gland fluid that is isotonic and reflects an ultra-filtrate of plasma (Mircheff, 1989). In support of this contention, tear fluid has been reported to be isotonic with plasma (Rolando and Zierhut, 2001); and, as such, it could be hypothesized that a progressive increase in plasma osmolality during hypertonic-hypovolaemia would be reflected in Tosm. Ductal cells comprise about 10–12% of the lacrimal gland, are estimated to contribute about 30% of lacrimal gland fluid, and

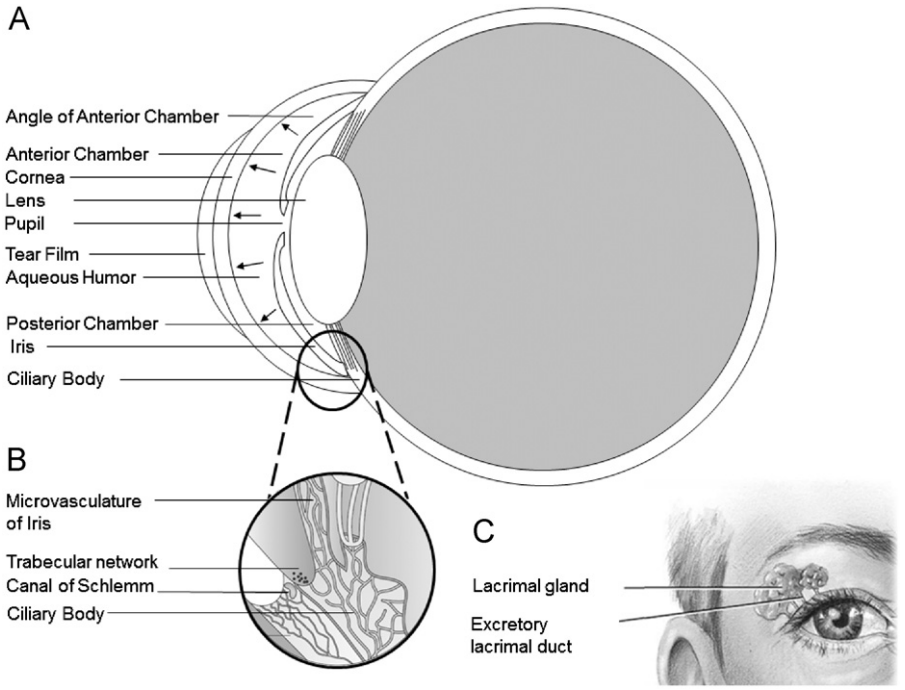

Fig. 1. (A) A simple cross-sectional eye schematic illustrating key parts of ocular anatomy. Intraocular pressure (IOP) is indicated by outward facing arrows in the anterior chamber. (B) Close-up of the aqueous humor drainage system. Aqueous humor drains through the trabecular network into the canal of Schlemm. (C) Depiction of the lacrimal gland.

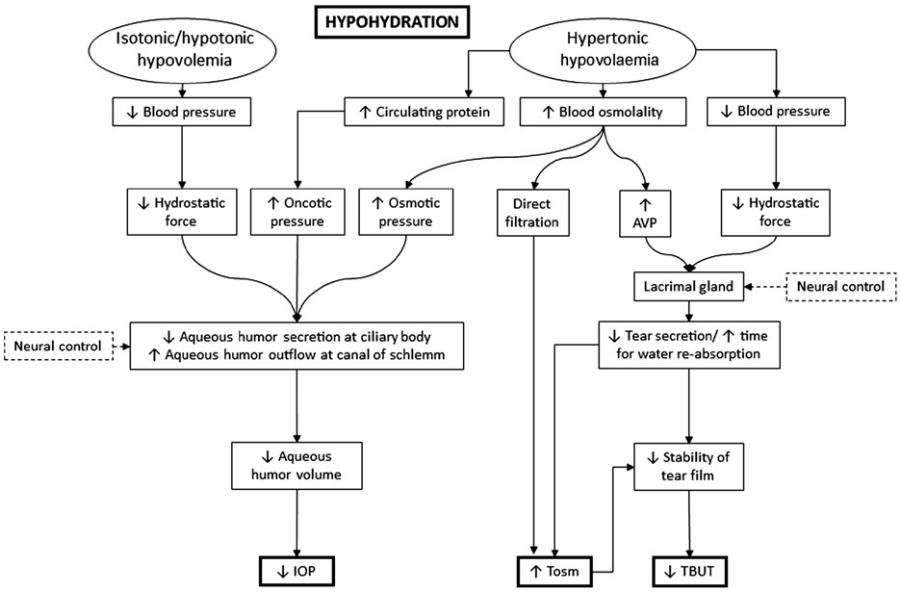

Fig. 2. Possible pathways by which hypohydration may alter intraocular pressure (IOP), tear break-up time (TBUT) and tear osmolarity (Tosm). Neural control is shown at the level of the lacrimal gland and ciliary body in a box with a dashed line as this is likely to be independent of hydration. AVP=arginine vasopressin.

their main role is to modify the primary lacrimal gland fluid by secreting electrolytes and water before transporting the lacrimal gland fluid to the ocular surface (Dartt et al., 1981). Dense innervation of the lacrimal gland by parasympathetic nerves (Dartt et al., 1984) and the overwhelming evidence that loss of parasympathetic innervation blocks lacrimal gland function (Dartt, 2009) supports a predominant role for parasympathetic activity over sympathetic activity in lacrimal gland fluid secretion. The total volume of tear fluid in the external eye is ~10 μl and unstimulated tear secretion has been reported to be between 0.15 and 1.2 ml each day (Mathers and Daley, 1996; Tiffany, 2008). A continuous tear film is required to fulfill its protective role, thus thinning or breaking (i.e. rupture) of the tear film (tear break-up) produces an irregular surface appearance. Autonomic blinking serves as a way of rinsing and reforming the tear film. The stability of the tear film is important for eye health and is governed by its surface and chemical characteristics. The precise mechanism underlying tear break-up is not known. Several competing theories exist to explain the phenomenon of tear break-up and the importance of the aqueous layer in stabilising the tear film is well accepted (Holly and Lemp, 1977; Ruckenstein and Sharma, 1986; Wong et al., 1996).

A typical tear film (Fig. 1A) is 7–9 μm thick with ~90% attributed to the aqueous layer (Patel and Blades, 2003; Ruckenstein and Sharma, 1986; Wong et al., 1996). However, reported values as low as 3 μm (King-Smith et al., 2000) and as high as 40 μm (Prydal et al., 1992) have shown a discrepancy to the typical tear film model. A thicker tear film is more stable (Wong et al., 1996), but changes in the thickness of the aqueous layer cannot be measured directly. Although there are numerous tests available to assess tear volume and flow, they are either invasive (require surface contact with the eye) or highly subjective measures with inadequate resolution for measuring small changes in tear thickness common to marginal dry eye (Patel and Blades, 2003).

An inadequate tear film can however, be evaluated using tear film stability tests, such as noninvasive tear break-up time (NITBUT) or the slightly more 'invasive' tear break-up time (TBUT). Tear break-up time is defined as the elapsed time between a complete blink and the appearance of a 'break' in the tear film is detected and is typically recorded in seconds. Changes in tear film stability have been measured in response to mild dehydration (Kayikcioglu et al., 1998) under the presumption that a decrease in total body water (TBW) may reduce aqueous layer formation (Fig. 2).

Alterations in hydration status may also affect aqueous humor formation. The amount of aqueous humor present in the anterior chamber is dependent on the rates of inflow and outflow (Connors, 2009). Both of these variables are influenced by a host of factors including the effects of various pressures (hydrostatic, oncotic and osmotic) (Fig. 2), anatomical considerations, the most important of which appear to be structures of the ciliary body in the posterior chamber, and of the angle of the anterior chamber (Fig. 1B).

The ciliary body is located at the root of the iris and is the source of the aqueous humor. The aqueous humor flows from the back of the iris in the posterior chamber through the pupil and into the anterior chamber. The angle of the anterior chamber houses the main portals that allow outflow of the aqueous humor such as veins in the ciliary muscle (uveoscleral route) and the canal of Schlemm, which leads to the episcleral veins (Oyster, 1999). Because the aqueous humor is a fluid that is confined to a limited space, it exerts pressure on the surrounding walls in which it is confined. This is known as intraocular pressure (IOP) and serves the purpose of giving shape to the eye in the anterior chamber (Connors, 2009). The process of aqueous humor production by the ciliary body is under tight neuro-endocrine regulation and out-flow at the canal of Schlemm is largely controlled by parasympathetic and sympathetic nervous activity (Coca-Prados and Escribano, 2007) that is likely to be largely independent of changes in whole body hydration (Fig. 2). Nevertheless, due to the intricate relationship exhibited between the various forces that accompany hypohydration, it is quite possible that significant changes in TBW may produce detectable changes in IOP (Fig. 2).

3. Tear fluid osmolarity (Tosm)

Measurement of Tosm can be made on a small tear fluid sample of 0.1–0.2 μL using freezing-point depression or vapor-pressure osmometers. In healthy individuals, Tosm is normally between 275 and 308 mOsm L^{-1} (Lemp et al., 2011). Previously, studies report large variability (Benjamin and Hill, 1983; Gilbard et al., 1978) that is likely due, at least in part, to inadequate

sample volume and evaporation of tear fluid in the 3–5 min delay from collection to measurement (Tiffany, 2008). Until very recently, another obstacle to the general application of Tosm measurement was the need for an experienced investigator who could obtain the tear fluid without disturbing its basic composition: reflexive tearing can alter tear fluid composition (e.g. Tosm) (Nelson and Wright, 1986). Common tear collection techniques such as using glass capillary tubes or absorbing Schirmer papers are uncomfortable, time-consuming and technically demanding procedures that may irritate the ocular surface and initiate reflex tearing (Esmaeelpour et al., 2008). Very recently, a non-invasive tear collection and analyzing device has made it possible to measure Tosm on a very small sample of tear fluid (50 nL) (Benelli et al., 2010). The TearLab® osmolarity system utilizes a single-use test card mounted on a hand-held pen, which both collects the sample and initiates the measurement (Fig. 3). The collection procedure is performed by resting the tip of the test card on the lower tear meniscus, which takes only a few seconds, is painless and requires little technical expertise; indeed, it is possible to perform the collection on oneself looking in a mirror. The pen is immediately docked onto the TearLab® platform where an output is generated within 10 s using the principle of electrical impedance.

Using the TearLab® osmolarity system, one recent study showed that increases in plasma osmolality during exercise-evoked dehydration and subsequent overnight fluid restriction were reflected in increases in Tosm (Fig. 4) (Fortes et al., 2011). In addition, decreases in plasma osmolality during a fluid intake trial were also reflected in decreases in Tosm providing confidence that the changes in Tosm reflect changes in hydration and not an exercise artefact (Fortes et al., 2011). A large correlation was observed between Tosm and plasma osmolality ($r=0.72$, $P<0.01$), however the mechanism(s) for the observed association of Tosm and plasma osmolality remains to be elucidated (Fortes et al., 2011) (Fig. 2); for example, it remains a matter of contention whether tear fluid represents a direct filtrate from plasma (Ubels et al., 1994). Using Tosm as a hydration assessment tool may be especially appealing to clinicians because the procedure is less-invasive compared with plasma osmolality, requires little expertise to perform, and provides a rapid reading. Biological variation analysis also suggests that Tosm change values may be diagnostically useful for hydration assessment (Fortes et al., 2011). It remains to be seen how Tosm responds to isotonic-hypovolaemia or if it can be applied successfully in an outdoor sports medicine setting where sunlight, wind, movement convection, sweat (in the eyes) and other factors may complicate Tosm measurements.

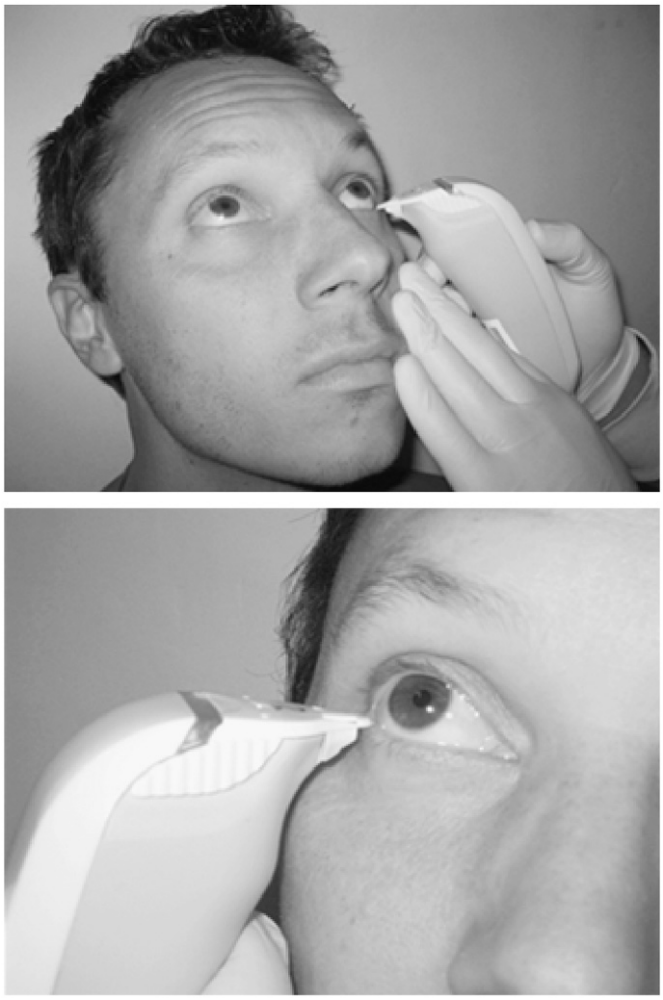

Fig. 3. Tear fluid collection procedure using the TearLab® osmolarity system. Reprinted with permission (Fortes et al., 2011).

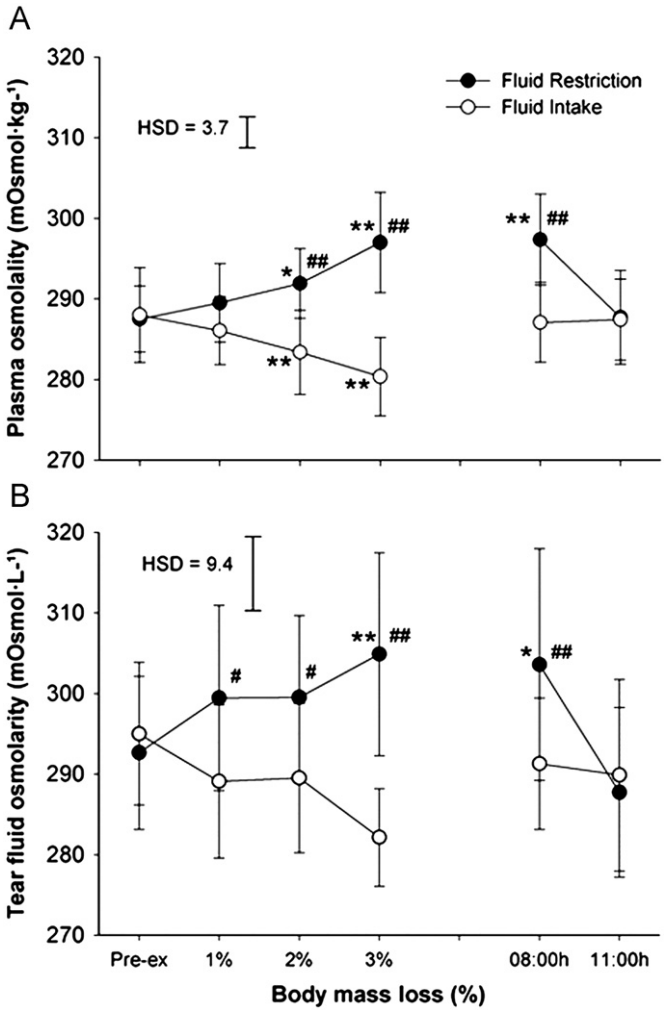

Fig. 4. Plasma osmolality (A) and tear osmolarity (B) responses to progressive exercise-heat induced dehydration to 1%, 2% and 3% body mass loss, subsequent overnight fluid restriction (08:00 h) and rehydration (11:00 h) during fluid restriction (FR ●) and with fluid intake to offset fluid losses (FI ○). Values are means and SD ($n=14$). HSD indicates Tukey's honestly significant difference value ($P<0.05$). Significantly different from pre-exercise ($^{*}P<0.05$, $^{**}P<0.01$). Significant between trial differences ($\#P<0.05$, $\#\#P<0.01$). Reprinted with permission (Fortes et al., 2011).

4. Tear break-up time (TBUT)

The time a tear takes to break-up, which is also an indicator of tear film stability, can be assessed via two main methodologies. One version is invasive (TBUT) while the other is non-invasive (NITBUT). Both assessments depend on the same underpinning physiology. The criterion measure is NITBUT (Holly and Lemp, 1977; Norn, 1986; Patel and Blades, 2003). The Keeler Tearscope-Plus® is one type of hand-held slit lamp that can be used to assess NITBUT when combined with magnifier and coarse grid accessories (Guillon, 1998). The principle of operation relies on the intact tear film acting like a mirror upon which a grid image can be projected. A thinning (or break) of the tear film is detectable as random distortions or discontinuities in the grid image. The time interval between a blink and the first appearance of grid distortion is taken as the NITBUT (Guillon, 1998; Mengher et al., 1985a; Patel and Blades, 2003). On the other hand, TBUT is the measure whereby a fluorescein stain is utilized to visualize the break in the tear film. This stain tends to decrease tear film stability thus shortening the time reported compared to NITBUT (Mengher et al., 1985b; Norn, 1969). In one study, where both measures were obtained on the same individuals, TBUT and NITBUT were not in agreement (Cho and Douthwaite, 1995). NITBUT of 20–30 s is considered normal and a time of ≤ 10 s is also used as a threshold for clinical dry eye diagnosis (Mengher et al., 1986). However, reported TBUT varies within the literature based upon methodology (Cho et al., 1992), ethnicity (Cho and Brown, 1993), diurnal variation (Patel et al., 1988), recovery from eye surgery (i.e. Lasik) (Albietz et al., 2002; Aras et al., 2000) and the choice of which eye is used first in assessment. The choice of which eye is tested first can confound results since the duration of eye opening influences subsequent reflex tearing (Mengher et al., 1985a,b). All of these variables lead to equivocal conclusions regarding the reliability of TBUT assessment for clinical purposes.

In an eye with otherwise healthy mucous, aqueous, and lipid layers, a reduction in TBW might impair lacrimal function and shrink the aqueous tear layer enough to decrease TBUT (Fig. 2). If dehydration were to reduce the aqueous layer to 1 μm thickness, the undermined tear stabilising influence of Marangoni-flow, which is generated from surface tension gradients, would reduce TBUT by 30%, similar to values observed with aqueous deficient dry eyes (Lemp et al., 1971). Indeed, while 'dry eye' is a common medical condition with a multitude of potential causes, abnormalities in lacrimal gland secretion explains the etiology of aqueous deficient dry eye (Holly and Lemp, 1977; Patel and Blades, 2003). Sjögren's syndrome is an extreme example of an autoimmune disorder that attacks moisture-producing glands like those of the mouth (salivary) and eyes (lacrimal), resulting in both dry mouth and dry eyes syndromes. The absence of tears in crying children (<3 years old) is also among the top four clinical predictors of severe pediatric dehydration (Friedman et al., 2004). However, the only study (Kayikcioglu et al., 1998) that examined the effects of dehydration on tear break-up time found no effects but the level of dehydration was marginal (-1.5% body mass) and the choice of TBUT technique (fluorescein stain) may have artificially shortened the tear break-up time (Mengher et al., 1985b; Norn, 1986), thus masking any effects. Therefore, since no investigations have examined NITBUT, careful assessments using this methodology should be carried out to determine if NITBUT is predictably altered by hypohydration. Based upon the list of confounding variables presented and the inherent variability within the measure (Brown and Cho, 1994; Cho, 1993; Cho and Douthwaite, 1995), NITBUT would appear to have greatest potential for dynamic hydration assessment.

5. Intraocular pressure (IOP)

IOP can be measured through multiple methods all of which utilize the same underlying principal. IOP measurement is accomplished by deforming the cornea with the presumption that the higher the IOP, the harder the cornea will be to deform via a forward pressing force from a finger, plunger or a puff of air (Oyster, 1999). The most common assessment, which is considered the criterion measure, is the Goldmann tonometer (Kass, 1996). The Goldmann tonometer is not without limitations as it requires an expert to make the measurements as well as a topical anesthetic (fluorescein). However, recently tonometers that are less invasive and are more user friendly (not requiring a medical expert) have demonstrated promising results and these can be used in both lab and field settings (Abraham et al., 2008). IOP measurement is important during ocular examinations for presence of ocular hypertension (IOP ≥ 21 mmHg), which could be indicative of developing glaucoma (Hollows and Graham, 1966).

IOP in a normal population is approximately 16 ± 3 mm Hg, with a positive skew towards higher values (Hollows and Graham, 1966). A number of factors can affect IOP such as age (Hollows and Graham, 1966), diurnal variation (David et al., 1992; Henkind et al., 1973; Sacca et al., 1998; Wilensky, 1991), exercise intensity and modality (Risner et al., 2009), cold exposure (Ortiz et al., 1988), high altitude exposure (Bosch et al., 2010), change in PCO_2 (Hvidberg et al., 1981) and change in body position (Hvidberg et al., 1981). However, the most pertinent extrinsic factor is that acute fluid ingestion can increase IOP 2.2–2.7 mmHg, thus giving support for this measure's potential to assess hydration status (Brucculeri et al., 1999; Drance, 1963; Martin et al., 1999; Moura et al., 2002; Read and Collins, 2010).

In a healthy eye, TBW reduction might result in a significant decrease in IOP due to the close association between compositional changes in blood and aqueous humor (Fig. 2) (Gaasterland et al., 1979). Thermal dehydration, resulting in hypertonic-hypovolaemia, will lead to increased plasma osmolality and increased total circulating protein concentration, which will lead to changes in both osmotic and oncotic forces, respectively (Ashkenazi et al., 1992). Furthermore, fluid and electrolyte losses resulting in isotonic-hypovolaemia lead to larger extravascular fluid losses (Mange et al., 1997; McGee et al., 1999), decreases in blood pressure and subsequent decreases in intraocular pressure from reduced hydrostatic forces. This is commonly seen after diuretic use, such as carbonic anhydrase inhibitors, which are commonly prescribed to glaucoma patients (van der Valk et al., 2005; World Heath Organization; 2009). Both types of hypohydration could affect aqueous humor formation/removal and inevitably influence IOP. Thus, hypohydration may decrease aqueous humor volume ('ocular dehydration') and consequently decrease IOP, which would enable this measurement to potentially assess both hypovolaemia subtypes. Currently, equivocal results have been published. In some studies the correlations between changes in IOP and changes in plasma osmolality (criterion hydration status measure) have been significant (Ashkenazi et al., 1992; Marcus et al., 1970; Stewart et al., 1970) while others have shown little promise (Brucculeri et al., 1999; Harris et al., 1994; Martin et al., 1999).

A recent pilot study from Hunt et al. (in press) has provided some evidence of an association between body mass loss (water loss) and change in IOP. These authors demonstrated a stronger relationship to body mass loss when the change in IOP (dynamic assessment) was used as compared to the absolute value (static assessment). These results provide direction for future experiments, however, careful consideration of the exercise protocol (Risner et al., 2009) and the effects of core body temperature need to be considered as both may independently affect IOP

(Hunt et al., in press; Moura et al., 2002; Shapiro et al., 1981). Lastly, conscientious consideration of the various confounders previously listed should be taken into account in the experimental design when testing IOP as a tool to assess hydration.

6. Conclusions

In summary, there is a relevant physiological basis for testing the merit of ocular measures (Tosm, NITBUT and IOP) for human hydration assessment. Recent data indicate that Tosm (Fortes et al., 2011) and IOP (Hunt et al., in press) may have utility for assessing hydration status, particularly in a clinical setting. The potential efficacy of NITBUT in a similar setting is logical, but untested. It remains to be seen how any ocular measure responds to isotonic-hypovolaemia or if they can be applied successfully in more austere outdoor settings where sunlight, wind, movement convection, sweat (in the eyes), and other factors may complicate these measurements. Further investigations are warranted to determine the degree to which ocular measures can act as accurate and reliable non-invasive hydration status markers.

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